IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Oliver Peoples, Lara L. Madison and Gjalt W. Huisman

Serial No.: 09/364,847 Art Unit: 1652

Filed: July 30, 1999 Examiner: D. Steadman

For: *ENZYMES FOR BIOPOLYMER PRODUCTION*

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-6 in the Office Action mailed February 12, 2003, in the above-identified patent application. A Notice of Appeal was mailed on May 12, 2003. A check in the amount of $160.00 for the filing of this Appeal Brief for a small entity is also enclosed.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee Metabolix, Inc.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-6 are pending. Claims 7-14 have been cancelled. Claims 1-6 are on appeal. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

An amendment after final rejection was mailed on May 12, 2003. In the Advisory Action mailed on May 29, 2003, the Examiner indicated that this amendment would be entered. An appendix sets forth the claims on appeal.

(5) SUMMARY OF THE INVENTION

The present invention is directed to protein fusions wherein the fusion has a formula selected from the group consisting of E1-Ln-E2 and E2-Ln-E1. E1 and E2 are expressed as catalytically active enzymes which act on substrate in successive reactions in a polyhydroxyalkanoate biosynthetic pathway (see, for example, page 5, lines 2-13) and are each selected from the group consisting of β-ketothiolases, acyl-coA reductases, polyhydroxyalkanoate synthases, poly(3-hydroxybutyrate) synthases, phasins, enoyl-coA hydratases, and beta-hydroxyacyl-ACP::coenzyme-A transferases (see, for example, pages 8-11, Section A; Figure 1, A-H; and page 4, lines 16-30). The linker L_n is a peptide of n amino acids that links the carboxyl terminus of E1 to the amino terminus of E2 or the carboxyl terminus of E2 to the amino terminus of E1 (see, for example, Examples 1 and 2; page 7, lines 15-21). E1

and E2 may be selected from the group consisting of β-ketothiolase (phbA) and acyl-CoA reductase (phbB); phbB and phbA; PHA synthase (phaC) and phasin (phaP); phaP and phaC; phaC and beta-hydroxyacyl-ACP::coenzyme-A transferase (phbG); phbG and phaC; phaC and enoyl-CoA hydratases (phaJ); and phaJ and phaC (see, for example, Examples 1-5; and Figure 1, A-H). The linker may be between zero and 50 amino acids and/or comprised of glycine-serine residues. The fusion may be expressed in a plant or in bacteria (see pages 13-16, Section II; and Examples 1 and 2).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claims 1-6 are enabled as required by 35 U.S.C. § 112, first paragraph;

(2) whether claims 1-6 are clear and definite as required by 35 U.S.C. § 112, second paragraph;

(3) whether claims 1-3, 5 and 6 were properly rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,245,023 to Peoples *et al.* ("Peoples"), in view of *Trends Biotechnol.* 9:226-231 by Bulow ("Bulow"); and

(4) whether claim 4 was properly rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,245,023 to Peoples *et al.* ("Peoples"), in view of *Trends Biotechnol.* 9:226-231 by Bulow ("Bulow") as applied to claims 1-3, 5 and 6 above, and further in view of *J. Mol. Biol.* 211:943-958 by Argos ("Argos").

(7) GROUPING OF CLAIMS

The claims do not stand or fall together. The claims can be grouped as follows: (1) claim 1, directed to protein fusions having a formula selected from the group consisting of E1-Ln-E2 and E2-Ln-E1, wherein each enzyme catalyzes substrate in successive reactions in a polyhydroxyalkanoate biosynthetic pathway and are each selected from the group consisting of β-ketothiolases, acyl-CoA reductases, polyhydroxyalkanoate synthases, poly(3-hydroxybutyrate) synthases, phasins, enoyl-CoA hydratases, and beta-hydroxyacyl-ACP::coenzyme-A transferases, in which linker L_n is a peptide of n amino acids that links the carboxyl terminus of E1 to the amino terminus of E2 or the carboxyl terminus of E2 to the amino terminus of E1; (2) claim 2, directed to defining each of the enzymes used in the fusion of claim 1; (3) claims 3 and 4, directed to defining the linker of claim 1; and (4) claims 5 and 6, directed to a host expression system for the fusion(s) of claim 1. Reasons for this grouping and arguments for the separate patentability of groups 2 and 4 are provided below.

(8) ARGUMENTS

(a) The Claimed Invention

The claimed invention is a fusion enzyme for the production of polymer, wherein each enzymatic portion of the fusion is a specific bacterial enzyme, and the polymer is polyhydroxyalkanoate. Once fused the enzymes remain catalytically active, and may be linked together *via* an amino acid linker connecting the carboxyl and amino termini of the respective enzymes. The appellants have provided Examples (see specification) demonstrating the expression of active polypeptides encoding multiple enzyme activities. The active polypeptides are homotetrameric enzymes which require the use of cofactors and which interact to synthesize

polymer, **which have not previously been demonstrated to be expressible as fusion proteins**. At least three extremely important activities are required to be successful for making and using the claimed protein fusions: 1) proper construction of the fusion at the genetic level in order to maintain proper folding of each protein/enzyme unit of the fusion (there are two of them: E1 and E2); 2) proper expression in order to generate enough fusion protein to assay activity; and 3) ensure proper transfer of substrate/product from one enzymatic domain to the next one of the fusion (this is assayed *via* the production of polyhydroxyalkanoate). The appellants have reduced each activity to actual practice.

(b) Rejections Under 35 U.S.C. § 112

i. The Legal Standard for Enablement

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d

1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). There is no requirement for examples.

ii. Rejection of Claims 1-6 under 35 U.S.C. § 112, first paragraph (enablement)

The invention is a protein fusion having a formula selected from the group consisting of E1-L_n-E2 and E2-L_n-E1, wherein E1 and E2 are expressed as catalytically active enzymes which act on substrate in successive reactions in a polyhydroxyalkanoate pathway. The genes, which are selected from the group consisting of β-ketothiolase (phbA) and acyl-CoA reductase (phbB);

phbB and phbA; PHA synthase (phaC) and phasin (phaP); phaP and phaC; phaC and beta-hydroxyacyl-ACP::coenzyme-A transferase (phbG); phbG and phaC; phaC and enoyl-CoA hydratases (phaJ); and phaJ and phaC, are known and publicly available. Medline and Genbank accession numbers disclosing sequences encoding these enzymes have been disclosed, as well as reference to specific journal articles (please see pages 8-10 of the specification; and pages 4-8 of the Response and Amendment mailed on December 27, 2002). Medline indicates that for each of these classes of enzymes, **the amino acid sequence and** a cDNA encoding the enzyme are known from multiple sources, but that the degree of homology is such that the known and available genes can be used to isolate additional genes from other sources encoding the enzymes. It is the amino acid sequence and protein function that allows for proper classification (i.e. synthase, hydratase, phasin, etc.). ***If others*** (i.e. other proteins) are desirable, one of ordinary skill in the art may isolate the necessary genes using any of a number of techniques, including the use of oligonucleotide primers *designed to be complementary to the known sequence* (and/or degenerate primers) in conjunction with, for example, polymerase chain reaction (PCR).

The present issue of enablement is this: having disclosed (*via* Examples) 1) the construction of thiolase-reductase protein fusions (Example 1); 2) the incorporation of a glycine-serine linker that connects the thiolase and the reductase enzymes (Example 1); 3) examination of the integrity of fusions at the polypeptide level in transformed cells *via* immunoblot and enzymatic assay (Example 1); 4) demonstrating active thiolase and reductase function of the fusion protein (Example 1 and Table 1); 5) the construction of reductase-thiolase fusion proteins (Example 2); 6) using PCR products to construct a reductase-glycine-serine-thiolase fusion

enzyme (Example 2); and 7) showing step-by-step protocol for the design and construction of PHA synthase-ACP::CoA transferase fusions (Example 3), PHA synthase-hydratase fusions (Example 4), and broad-substrate range thiolase-reductase fusions (Example 5); is the appellant entitled to claim protein fusions expressed as catalytically active enzymes which act on substrate in successive reactions in a polyhydroxyalkanoate (PHA) biosynthetic pathway and are each selected from the group consisting of β-ketothiolases, acyl-CoA reductases, polyhydroxyalkanoate synthases, poly(3-hydroxybutyrate) synthases, phasins, enoyl-CoA hydratases, and beta-hydroxyacyl-ACP::coenzyme-A transferases ? One of ordinary skill in the art will easily recognize that any asserted gaps between the present disclosure and claim breadth can be easily bridged; and will understand that any/all PHA biosynthetic enzymes that fall within each of the identified classes of enzymes (based upon already known amino acid sequence and function) could be used efficiently as reagents in constructing the claimed fusions. Furthermore, for one of ordinary skill in the art it is a relatively simple matter to determine whether a particular fusion, as claimed, is properly functional. Any challenge which one of ordinary skill in the art in 1998/1999 might have encountered in attempting to make and use the claimed invention using any enzyme within the protein classes defined in claim 1 (or DNA encoding the same), could be resolved by experimentation falling short of undue. Again, the appellants assert that the present disclosure of protein fusions as shown in the examples enables a broader genus under the circumstances. The differences between using/constructing thiolase-reductase protein fusions, reductase-thiolase fusion proteins, PHA synthase-ACP::CoA transferase fusions, PHA synthase-hydratase fusions, and broad-substrate range thiolase-reductase fusions; and other such

enzymes, or DNA sequences encoding the same, are small and easily accommodated by the artisan.

In view of the foregoing, it is worthwhile to briefly revisit two separate court rulings: 1) *Phillips Petroleum*, 865 F.2d at 1251, 9 USPQ2d at 1465, wherein the patentee was entitled to a prior filing date because the earlier disclosure of polypropylene as know that the time described and enabled a later claim to "normally solid polypropylene" even though a new, higher molecular weight form of polypropylene had been subsequently discovered; and 2) *Cellpro*, 152 F.3d at 1361, 47 USPQ2d at 1719, wherein the court affirmed summary judgment of enablement of a product claim over a challenge that two alternative embodiments disclosed in the patent were not enabled because "the enablement requirement is met if the description enables any mode of making and using the invention". It is clear that the appellant's have described and enabled at least five ways (thiolase-reductase, reductase-thiolase, PHA synthase-ACP::CoA transferase, PHA synthase-hydratase, and broad-substrate range thiolase-reductase; see Examples) to make the claimed invention; and at least two ways to test the claimed invention (immunoblot and enzymatic assay; see Examples). One of ordinary skill in the art would readily infer from the data presented in these Examples that similar outcomes would be expected from any/all fusions constructed from enzymes belonging to the claimed classes of proteins.

iii. The Legal Standard for Written Description

Both the written description and enablement requirements are defined by 35 U.S.C. § 112, first paragraph, which states that the patent specification must contain "a written description of the invention, and of the manner and process of making and using it...[such] as to enable any

person of ordinary skill in the art to which it pertains ... to make and use the same ... " The purpose of the written description requirement is to prevent a patentee from later asserting that he invented something which he did not. Thus the patentee must "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Vas- Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 U.S.P.Q.2d 1111, 1115 (Fed. Cit 1991). The purpose of the enablement requirement is to teach those of ordinary skill in the art how to make and use the invention without "undue experimentation." The specification does not need to teach what is already known in the art. The specification is enabled if one of ordinary skill in the art only engages in routine experimentation to make the invention.

For many years the leading case for the written description requirement in the biotechnology and pharmaceutical arts was *Eli Lilly v. Univ. of Calif. Board of Regents* In *Regents of University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089 (1998). The Federal Circuit evaluated whether claims to recombinant production of human insulin in U.S. Patent No. 4,652,525 (herein referred to as "the '525 patent") met the written description requirement. The court determined that the specification failed to comply with the written description requirement for only disclosing a single species of DNA encoding non-human insulin.

In *Enzo Biochem*, the Federal Circuit held that that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. *Enzo Biochem, Inc., v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir.2002) ("*Enzo II*"). The Federal Circuit held that a patentee

complied with the written description requirement by depositing biological material in a public depository. The specification described the nucleotide sequence in terms of its ability to bind to *N. gonorrhoeae*. The patent had issued with no written description rejection. Nevertheless, the Federal Circuit had determined in *Enzo I* that, because the inventor had not described the actual nucleotide sequence of the probes in the patent specification, the written description was inadequate as a matter of law. In *Enzo II*, the Federal Circuit rejected its narrow interpretation of *Eli Lilly* that the disclosure of the sequence was always necessary, and instead adopted a broader interpretation of the types of disclosures that comply with the written description requirement. The court adopted provisions from the Guidelines issued by the U.S. Patent and Trademark Office that state that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. The court found that the written description requirement was met when, in the knowledge of the art, the disclosed function is sufficiently correlated to a particular, known structure.

This standard has been reviewed and clarified further in the recent decision of *Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.* 314 F.3d 1313, 65 USPQ 2d (Fed. Cir. 2003). This decision was the appeal of a lengthy district court ruling on validity, infringement, and enforceability of five Amgen patents relating to production of erythropoietin (EPO), a hormone that controls formation of red blood cells. Amgen's EPO is sold under the brand name EPOGEN®. Amgen asserted that Hoechst (now Aventis Pharmaceuticals, Inc.) and Transkaryotic Therapies ("TKT") infringed U.S. Patent No. 5,547,933; 5,618,698; 5,621,080;

5,756,349; and 5,955,422, due to the filing of TKT's Investigational New Drug Application (INDA). All of the patents shared the same disclosure. TKT recombinantly produced EPO using a method that differed from the method used by Amgen and described in the patents. TKT inserted a promoter which caused the expression of ordinarily unexpressed endogenous (or "native") EPO DNA in human cells to produce the EPO.

The Federal Circuit upheld the lower court's claim construction and its decision that the claims comply with the written description and enablement requirements of 35 U.S.C. § 112. In rendering its decision, the Court continued in the manner of *Enzo II* and applied a broad interpretation of the types of disclosures that comply with the written description requirement. TKT asserted that claims did not meet the written description requirement since Amgen had failed to describe the use of all mammalian and vertebrate cells, relying on the earlier *Lilly* decision.

Relying heavily on the expert testimony provided in the District Court proceeding, the Federal Circuit held that this description adequately supports the claims covering EPO made using the genus vertebrate or mammalian cells.

One question that arose out of these proceedings was whether or not Amgen's disclosure of one means of producing synthetic EPO in mammalian cells, namely exogenous DNA expression, entitles it to claim all EPO produced by mammalian cells in culture, or all cultures vertebrate cells that produce EPO. The district court in this case found that "the specification need teach only one mode of making and using a claimed composition." *Amgen, Inc v. Hoechst Marion Roussel, Inc* 126 F.Supp.2d 69, 160, 57 USPQ 2d 1449, 1515 (D.Mass.2001).

iv. Claims 1-6 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey that the inventor had possession of the claimed invention at the time of filing.

As noted above, the court has adopted provisions from the Guidelines issued by the U.S. Patent and Trademark Office that state that the written description requirement *can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure.* In the present case, the enzymes are defined by their function (i.e. their ability to catalyze a reaction based on one or more appropriate substrates). As further discussed above, the appellants have reduced to practice all aspects required to make and use the presently claimed invention.

The claims of the present application refer to fusion proteins expressed as catalytically active enzymes which act on substrate in successive reactions in a polyhydroxyalkanoate biosynthetic pathway. The enzymes that make up each part of the fusion protein (excluding the linker), are well-known and exist within well-defined classes of proteins. The words "phasins", "thiolase", "reductase", "beta-hydroxyacyl-ACP::coenzyme-A transferase", and "enoyl-CoA hydratase" classify proteins and readily convey distinguishing information concerning identity, *via* structure and function, such that one of ordinary skill in the art could easily visualize the identity of the members of each classification. In contrast to the term, for example, "cDNA" in which one of ordinary skill in the art would have great difficulty in ascertaining an actual sequence, each of the above-identified classes of protein readily convey an appropriate level of

structure and function, especially in view of the sequences already disclosed in the specification and known in the art at the time of filing the present application.

One of ordinary skill in the art will absolutely agree that functional definitions **do** provide structural information commonly possessed by all members of each class. Over 30 years ago, Nobel Laureate Christian B. Anfinsen proved that a protein's "knowledge" of how to fold is stored in its sequence of amino acids. It is this fold that determines the protein's functionality (i.e. substrates recognized, reactions catalyzed, targeted protein binding, etc.). Conversely, a particular function can be directly attributed to particular folds determined by specific, or conserved, sequences of amino acids. It is well established in the art that structure –function relationships do exist, and it is no more prevalent than within families of proteins, such as those that drive the specific reactions of claim 1. The written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure.

(c) Rejections Under 35 U.S.C. § 103

i. The Legal Standard.

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention

would have a reasonable likelihood of success. *In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

The Court of Appeals for the Federal Circuit recently warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references." In re Dembiczak, 175 F.3d 994 at 999 (Fed. Cir. 1999). While the suggestion to combine may be found in explicit or implicit teachings within the references, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved, the "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. WMS Gaming, Inc. v International Game Technology, 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and

particular." In re Dembiczak, 175 F.3d 994 at 999 (Fed. Cir. 1999). Although with the answer in hand, the "solution" now appears obvious, that is not the test. The references must themselves lead those in the art to what is claimed. And in this case, there is simply no such teaching.

ii. The Prior Art.

Claims 1-3, 5 and 6 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,245,023 to Peoples *et al.* ("Peoples"), in view of *Trends Biotechnol.* 9:226-231 by Bulow ("Bulow").

Peoples

Peoples teaches the construction of polymerase fusions for the purpose of "altering the enzyme's specificity to create novel polymerases" (see column 23, lines 14-24). The protein fusions described in Peoples are directed to PHB polymerase and PHA polymerase genes. Such fusions would not catalyze successive reactions in a polyhydroxyalkanoate pathway, but ***alternative reactions - i.e., either addition of short chain or long chain substrate***. The claimed composition is the fusion of two enzymes that catalyze successive reactions in a polyhydroxyalkanoate biosynthetic pathway (i.e. each enzymatic "domain" of the fusion recognizes their normal (cognate) substrate). Therefore, the fusion enzyme of Peoples does not provide an indication of the success of a fusion enzyme that catalyzes the successive PHA biosynthetic reactions.

Bulow

Bulow teaches the optimal length linkers, for the enzymes described therein, based upon the correct folding and accessibility of active sites in the recombinant enzymes. Bulow's

statements relating to enzyme technology and its usefulness in the development of metabolic engineering are entirely prophetic (see entire last paragraph of Bulow). Such suggestions do not create an expectation of success without ***evidence*** suggesting the modification (i.e. fusion catalyzing **successive** reactions) would be successful (for example, see *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

iii. Summary

Peoples suggests the construction of a fusion between two polymerases (PHA and PHB) so that one could utilize more substrates **in the same reaction: the addition of monomer into the growing polymer chain.** Bulow teaches peptide linkers for use in making fusion proteins. No evidence has been provided to suggest that one skilled in the art would have an expectation of success in ***combining/*fusing** two catalytically active enzymes, **using different substrates, one of which produces the substrate for the second enzyme**, in a single fusion protein.

iv. Claim 4 was rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,245,023 to Peoples *et al.* ("Peoples"), in view of *Trends Biotechnol.* 9:226-231 by Bulow ("Bulow") as applied to claims 1-3, 5 and 6 above, and further in view of *J. Mol. Biol.* 211:943-958 by Argos ("Argos").

Appellant respectfully submits that in view of the foregoing discussion, as it relates to the rejection of claims 1-3, 5 and 6 under 35 U.S.C. § 103(a), the rejection of claim 4 is rendered moot.

(d) The Examiner has failed to individually examine the dependent claims

It is well established that each claim must be separately examined for patentability. It is not enough, as here, to look at a single independent claim and reject all claims. No rationale has been presented as to why the subject matter of claims 2, 5 and 6 (groups 2 and 4) are not enabled, or are not free from being obvious in view of prior art.

These claims must be considered separately because each group contains different elements (i.e. specific enzymes of claim 2 directed to successive reactions in a PHA biosynthetic pathway, and host systems for expression of the fusion). The issues are different with regard to enabling a fusion protein being expressed in host cells (claims 5 and 6). The issues are different with regard to enabling fusion proteins, wherein each enzymatic domain of the protein is different structurally and functionally. Furthermore, no art has been cited to show that the fusions of claims 5 and 6, in a host bacterium or plant, would be obvious to one of ordinary skill in the art. No art has been cited to show that the enzymes of claim 2 (catalytically active in a fusion protein) would be rendered obvious. Therefore, at a minimum, claim 2, and claims 5 and 6, should be recognized for separate consideration.

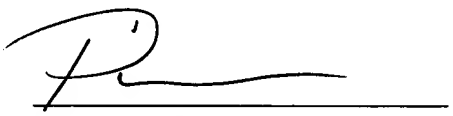
(9) SUMMARY AND CONCLUSION

As stated above, at least three extremely important activities are required to be successful for making and using the claimed protein fusions: 1) proper construction of the fusion at the genetic level in order to maintain proper folding of each protein/enzyme unit of the fusion (there are two of them: E1 and E2); 2) proper expression in order to generate enough fusion protein to assay activity; and 3) ensure proper transfer of substrate/product from one enzymatic domain to the next one of the fusion (this is assayed *via* the production of polyhydroxyalkanoate). In view

of the foregoing discussion, relating to enablement and written description, the appellants submit that the claimed fusions are enabled and the claims are properly supported by a more than sufficient specification in combination with the knowledge one of ordinary skill in the art would have had at the time of filing the present application. As far as the claimed invention being obvious or not, the appellants respectfully submit that suggestions made by Bulow and Peoples do not render the claimed fusion proteins obvious. Successful construction and expression of fusion proteins that catalyzed successive reactions in a polyhydroxyalkanoate biosynthetic pathway could not have been expected in view of the prior art alone. Only in hindsight of the present application, could one of ordinary skill in the art have realized the claimed fusion proteins.

For the foregoing reasons, Appellant submits that the claims 1-6 are patentable.

Respectfully submitted,



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Aisha Wyatt

Date: July 14, 2003

Appendix: Claims On Appeal

1. (twice amended) A protein fusion having a formula selected from the group consisting of E1-L_n-E2 and E2-L_n-E1, wherein E1 and E2 are expressed as catalytically active enzymes which act on substrate in successive reactions in a polyhydroxyalkanoate biosynthetic pathway and are each selected from the group consisting of β-ketothiolases, acyl-CoA reductases, polyhydroxyalkanoate synthases, poly(3-hydroxybutyrate) synthases, phasins, enoyl-CoA hydratases, and beta-hydroxyacyl-ACP::coenzyme-A transferases, in which linker L_n is a peptide of n amino acids that links the carboxyl terminus of E1 to the amino terminus of E2 or the carboxyl terminus of E2 to the amino terminus of E1.

2. (previously amended) The fusion of claim 1 wherein E1 and E2 are selected from the group consisting of β-ketothiolase (phbA) and acyl-CoA reductase (phbB); phbB and phbA; PHA synthase (phaC) and phasin (phaP); phaP and phaC; phaC and beta-hydroxyacyl-ACP::coenzyme-A transferase (phbG); phbG and phaC; phaC and enoyl-CoA hydratases (phaJ); and phaJ and phaC.

3. (original) The fusion of claim 1 wherein n in the linker is between zero and 50 amino acids.

4. (previously amended) The fusion of claim 1 wherein the linker is comprised of glycine-serine.

5. (original) The fusion of claim 1 expressed in a plant.

6. (previously amended) The fusion of claim 1expressed in bacteria.

7-14 (previously canceled)

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iv. Rejection of Claim 4 under 35 U.S.C. § 103(a)

(d) The Examiner has failed to individually examine the dependent claims

(9) SUMMARY AND CONCLUSION

Certificate of Mailing

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